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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/767,718	01/30/2004	Hideaki Hosokawa	000683A	6057

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/767,718	HOSOKAWA ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-56* is/are pending in the application.

4a) Of the above claim(s) *45-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/954,577.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/30/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The Election filed on 10/27/2006 in response to the Restriction Requirement of 9/29/2006 has been entered. Applicant's election, without traverse, of Group I, claims 31-44, as specifically drawn to a method of detecting cancer, wherein the protein capable of recognizing a specific modified sugar chain structure of carcinoembryonic antigens is an antibody has been acknowledged. Applicant's election of Anti-Le^a antibodies as the species for prosecution on the merits is acknowledged.

The restriction requirement is therefore deemed to be proper and is made FINAL.

Claims 31-56 are currently pending.

Claims 45-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions.

Claims 31-44 are currently under consideration.

Species Election

The Examiner has withdrawn the species election set forth in the prior office action.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/954,577, filed on 6/15/2000.

Information Disclosure Statement

The Information Disclosure Statement filed on 1/30/2004 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

Specification

The disclosure is objected to because of the following informalities: The specification appears to have numerous typographical errors. For example, Page 11, last line, recites a "m thod of using a labeled sp cific sugar biding". It is suggested that the last line of page 11 recite "a method of using a labeled specific sugar chain binding".

Appropriate correction is required.

Applicants are reminded that no new matter should be introduced by amendment to the specification, see MPEP 35 USC 132.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-44 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a correlation between the method steps and the preamble. For example, it is unclear what "ratio" is indicative of cancer.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

The claims encompass using proteins, which are capable of recognizing a specific modified sugar chain structure of carcinoembryonic antigens. Therefore, the claims encompass a genus of molecules defined solely by its principal biological property, which is simply a wish to know the identity of any material with that biological property. In the instant case, the specification teaches proteins which recognize a sugar chain containing a fucose residue and/or a sialic acid residue (page 6, last paragraph of specification). However, the specification appears to be silent on what is encompassed by a specific modified sugar chain structure of carcinoembryonic antigens. Accordingly, there is insufficient written description encompassing a "specific modified sugar chain structure of carcinoembryonic antigens" because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of a "specific modified sugar chain structure of carcinoembryonic antigens" are not set forth in the specification as-filed; and therefore, is not commensurate in scope with the claimed invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function" and the

expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity and which therefore, fails to satisfy the written description requirement. Similarly, a specific modified sugar chain structure of carcinoembryonic antigens which is recognized by a protein does not distinguish any particular specifically modified sugar chain structures of carcinoembryonic antigens from others having the same activity or function and as such does not satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

In the absence of structural characteristics that are shared by members of the genus of a "specific modified sugar chain structure of carcinoembryonic antigens"; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Claims 31-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative

skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of detecting a cancer comprising using a ratio of carcinoembryonic antigens having a specific modified sugar chain structure or carcinoembryonic antigens having the sugar chain structure other than the specific one relative to the amount of total carcinoembryonic antigens. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of detecting cancer comprising adding to partitioned samples; first, second, third, or fourth proteins which selectively bind to different sugar chain structures further including an antibody to a constant region of CEA and determining a ratio of carcinoembryonic antigens having a specific modified sugar chain structure or carcinoembryonic antigens having the sugar chain structure other than the specific one relative to the amount of total carcinoembryonic antigens, wherein the ratio is the indicator for the detection. Thus, the claims encompass any and/or binding molecules including antibodies.

Guidance in the specification and Working Examples

The specification teaches (page 7, last paragraph) that the specific sugar chain binding protein includes, for example, an antibody and a lectin. The specification goes on to list (pages 7- 8) the wide variety of both antibodies or lectins that may be included which selectively bind to different sugar chain residues. However, the specification teaches (page 21), that with regards to detecting cancer, one must employ the "proper combination" of the total amount of CEAs, and an amount of the CEAs having a "specific" modified sugar chain structure, and an amount of the CEAs having a sugar chain structure "other than the specific one". Moreover, the specification teaches that particular types of cancer can be determined by conducting the measurement with the use of "plural" kinds of *specific* sugar chain binding proteins and analyzing the results. The specification further teaches (page 25), with regards to the detection of cancer, antibodies against any one of S-Le^a, S-Le^x, Le^a and Le^y were added to a reaction sample containing a standard amount of antibody-labeled CEA. With regards to the sample, the specification teaches that sera was obtained from nine cancer patients and four from normal human beings, wherein the cancer includes rectal cancer, rectum cancer, lung cancers, liver cancer, oropharyngeal cancer, breast cancer, cerviz uteri cancer and metastasis of bone marrow lymph node (page 25, Samples and Table I). The specification further teaches (Table 1) that a ratio was determined which compared the amount of the CEAs reacted to a *specific* anti-sugar chain antibody relative to the amount of total CEAs (presumably, the total CEAs being the combination of the standard CEA plus any CEA derived from the human samples). For example, to determine rectal cancer, there must exist a certain percentage of S-Le^a and Le^a compared to total CEAs in the sample.

Quantity of experimentation

The quantity of experimentation is extremely large given the unpredictability of diagnosing cancer by measuring carbohydrate epitopes on the CEA molecules due to the heterogeneity associated with carbohydrate epitopes on the CEA molecules in a single patient serum and further, the lack of guidance necessary for one of skill in the art to predictably detect cancer because it appears that the method is limited to a particular combination of anti-sugar antibodies, not just any lectin or protein. In other words, the method is specific for the selection of a defined protein which recognizes a specific sugar chain residue on CEA... not any and all sugar chain residues as broadly claimed. As such, it would require undue experimentation for one of skill in the art to simply test the thousands of proteins which bind to different sugar chain residues in order to detect a particular type of cancer absent the information disclosed in Table I. Furthermore, simply "detecting" if a complex if formed between a first protein which binds to a sugar structure and an antibody to CEA and "detecting" if a complex is formed between a second protein (which binds to a different sugar chain structure than said first protein) and an antibody to CEA in order to determine the presence of a particular cancer based on whether said complexes are detected is beyond the scope of the disclosure. The guidance necessary to detect a particular type of cancer is highly specific to the determined **ratio** of specific anti-sugar chain antibodies relative to the total amount of CEAs.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that tumor markers such as CEA are useful in evaluating tumor burden and prognosis. For example, Nichols et al. (Journal of Immunol. 1985; 135: 1911-1913) teaches that plasma CEA levels are often elevated in patients with cancer; thus, CEA measurements have become useful in the management of human malignancies (page 1911, 1st column, 1st paragraph). Like wise, Tannock *et al.* (The Basic Science of Oncology, 2nd Edition, McGraw-Hill, Inc. 1992, pages 201-204) teach that in patients who have undergone surgery for breast cancer, CEA can be used as an independent predictor of relapse. In addition to the peptide portion of CEA being useful for diagnosis, Nichols et al. further teach that carbohydrate markers associated with cardinoembryonic antigens are also useful for enhancing the diagnostic value of the antigen. In particular, Nichols et al. teach (page 912, 2nd column, last paragraph) teach that the use of a combination of anti-CEA and anti-Y antibodies to detect both CEA polypeptides and carbohydrate determinants will be a more useful way of defining exactly the

specific CEA molecules than the existing method for CEA detection. Thus, while considerable research has gone into using a combination of anti-CEA and antibodies directed to the carbohydrate structure of CEA, those of skill in the art recognize the unpredictability associated with homogeneity of carbohydrate epitopes on the CEA molecules in a single patient serum. For example, Matsunaga et al. (Cancer Research 1987; 47: 56-61) analyzed the antigenic heterogeneity of CEA in serum from patients with various malignant diseases using six mouse monoclonal antibodies, two reactive with the peptide portion and 4 with carbohydrate moiety of CEA (page 58, 1st column, 1st full paragraph+ and page 59, Table 3). Specifically, Matsunaga et al. found that the 4 antibodies recognizing the carbohydrate epitopes were quite variable from case to case, wherein some patients sera reacted with all 4 of the antibodies; but some sera reacted with 1, 2 or 3 of them; and some other sera did not react with any of them at all (page 58, 2nd column, 1st paragraph, see Table 3). In addition, Kobata et al. (Pure & Appl. Chem. 1995; 67: 1689-1698) teaches the sugar chain structures of carcinoembryonic antigen obtained from three patients having liver metastases of colon carcinoma (page 1960, 1st full paragraph). Specifically, Kobata et al. found that Lewis x, Lewis a, Lewis y and Lewis b antigens are all glycosylated forms of carcinoembryonic antigen. However, like Matsunaga et al., Kobata et found that presence of the sugar chain structure on CEA varied from patient to patient, wherein one patient had all 4 and the other two had three with only two being the same (page 1696, Table III). Thus, in view of these references, one of skill in the art would recognize that glycosylation patterns obtained from a single patients sera would not be indicated of all patients serum.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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